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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
09/719,067	08/16/2001	David B. Weiner	UPN-3695	4038

34136 7590 03/27/2003

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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,067	WEINER ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants' response and amendments filed 1-6-03 have been entered.

2. Claims 1-29 are pending. Applicant's elected CD156 promoter in Paper No. 9.

3. The abstract has been entered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3 and 5-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method of delivering a protein to a macrophage cell or a cell of macrophage derived lineage, does not reasonably provide enablement for an in vivo method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 9-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention is directed to a method of delivering a protein to a lymph node, a method of producing an immune response against an immunogen, a method of modulating an individual's immune system, a method of eliminating cells in a lymph node of an individual and a method of delivering a desired protein to an individual or a macrophage or cell of macrophage lineage in vivo. However, the specification as filed does not provide sufficient guidance as to how an artisan of skill would have made and used the claimed invention. . An artisan of skill would have required undue experimentation to practice the claimed method because,

while the claimed method is directed to delivery, the purpose of the method is for treatment and immunization and the art of in vivo gene therapy was unpredictable at the time of the art and the specification as filed does not provide sufficient guidance as to how an artisan of skill would have addressed the art recognized limitations and unpredictability of the method.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification in figures 1-6 show results of eliciting immune response in a mice administered a pcGag/Pol, where the expression of the Gag/pol genes is under the CMV promoter, not a macrophage specific promoter. Figure 7 is a diagrammatic representation of a plasmid called pNeZCD3alpah.1, however, it is not clear as to what encoding sequence was used in this vector. Figure 9 compares difference in Nef mediated antibody production when Nef was under CMV promoter compared when under CD3 promoter. Looking as the figure, an artisan would think that there was no difference between CMV promoter and CD3 promoter. Specification in general provides a list of genes whose promoters could be

encompassed by macrophage specific promoter and the list includes all the possible CD genes, chemokines, or molecules involved in the immune system (see page 8, lines 18-31 continued on page 9, lines 1-8). The specification does not provide any specific guidance or structure of these promoters, what sequences will be required for the promoter function etc. In other words, an artisan would not know, what parts of the promoter or what parts of the regulatory sequences to use in making an expression vector. The specification does not provide any specific guidance as to what amount of plasmids or vectors will be administered, rather the specification does not provide any specific guidance to practice the claimed method. Therefore, an artisan of skill would have depended on the art for practicing the claimed methods and as discussed below the art of in vivo gene delivery and gene therapy is unpredictable, particularly vector construction and design. It is noted that claims are also directed to administration of a vector to lymph nodes at any site so that the vector is administered to the lymph nodes, however, the specification does not teach any specific description of where and how the administration will be carried out. It is pointed out that while the claimed invention recites macrophage specific promoters, one major issue is what vector will be used such that the administration to a subject was effective and was able to deliver the vector to macrophages. The specification does not provide any specific teachings as to what vectors will be suitable for this specific purpose.

Crystal (Crystal RG. Science 270:404-410.1995) assessed the state of the art of the gene therapy at the time the claimed invention was made. In the abstract, Crystal states "human gene therapy still faces significant hurdles before it becomes an established therapeutic strategy. " Later on page 409, he summarizes the problems faced in the art of gene therapy, such as inconsistent results, extrapolation of studies in mice to humans, production, and vector. He states " all of the human gene transfer studies have been plagues by inconsistent results, the bases of which are unclear" (see para 3 in col 1 on page 409). He also adds that there are several examples wherein prediction of gene transfer studies in experimental animals have not be borne out in human trials (see para 4 in col 1 on page 409). He also raises the issue of production of vectors, free of aggregation,

contamination and variability from preparation to preparation, some of the problems that must be overcome before large clinical trials can be initiated. Additionally, there is the issue of an ideal vector? Crystal argues that an ideal vector for gene therapy is conceptually impractical because the human applications of gene transfer are broad and the ideal vector will likely be different for each application (see col 2 on page 409).

Anderson (Anderson WF. Nature 392 (SUPP):25-30, 1998) notes that since the approval of first clinical trial of gene therapy protocol in 1990, more than 300 protocols have been approved worldwide. He further adds, "The conclusions from these trials are that gene therapy has the potential for treating a broad array of human diseases and that the procedure appears to carry a very low risk of adverse reactions; the efficiency of gene transfer and expression in human patients is, however, still disappointingly low. Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease."

Finally, Clay et al (Clark TM et al. Pathology Oncology Research 5:3-15, 1999) look at the some of the technical and biological hurdles that need to be addressed in gene therapy trials and conclude "Unfortunately, no gene therapy trial to date has been conclusively proven to be effective in treating the targeted disease.....It is clear that greater emphasis should be placed in vector development and understanding the biology of gene therapy targets if we expect gene therapy to be a viable option in the future..... Further advances will also be required in vector development and in establishing the optimum transduction conditions for target cells to enhance the efficiency of gene transfer and to provide prolonged gene expression."

It is noted that these reviews by the leaders in the field of gene therapy are about those gene therapy protocols and applications where the mechanism of action and some efficacy has been determined in animals models and there may be some extrapolatable correlations indicating the therapeutic effects of a particular gene's encoded protein. Even with such results, it is uncertain whether there would

be a therapeutic effect when the studies obtained in a mouse model or another animals model is extended to a human subject.

It is emphasized that while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art, which show promise, but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

As discussed above, while the instant invention is directed to methods using macrophage specific promoters, the specification does not provide any specific guidance as to how to make the vectors and practice the claimed methods. In conclusion, the art of gene therapy is highly unpredictable in general. Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect.

The courts have stated that reasonable correlation must exist between scope of a right to exclude a patent application and scope of enablement set forth in patent application. 27USPQ2d 1662 *Ex parte Maizel*.

In conclusion, limiting the scope of the claimed invention to an in vitro method is proper.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Malik et al (Blood 86:2993-3005, 1995).

Malik et al teach a comparison of hematiopoietic cell promoters to that of viral promoters, using retroviral vectors. For example, the art teaches comparison of CD11b, Cd18, CD34 genes (see the abstract and also the methods section).

Accordingly, the method of claims 1-3 and 5-7 is anticipated by Malik et al.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-3 and 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malik et al in view of Dropulie et al (US Patent 5,888,767, March 30, 1999, effective filing date 11-28-1996), Kataoka et al (Journal of Biological Chemistry 272:18209-18215, 1997) and Horvai et al (Proc. Natl. Acad. Sci. 92:5591-5393, 1995) .

Malik et al teach a comparison of hematiopoietic cell promoters to that of viral promoters, using retroviral vectors. For example, the art teaches comparison of CD11b, Cd18, CD34 genes (see the abstract and also the methods section). This art does not teach promoters of scavenger receptor or CD156 reporter.

Horvai et al teaches that Scavenger receptor gene a promoter targets gene expression to macrophages and to foam cells of atherosclerosis. The art also teaches this promoter might be used to direct to expression of a recombines, growth factors, enzymes or other molecules of physiological or pathological consequences to macrophages to determine their influence on development or treatment of atherosclerosis (see pages abstract, methods and discussion section). Kataoka et al teach structure and characterization of CD156 gene and that the promoter of this gene contains sequence regulatory elements that target expression of genes to myeloid cell-specific expression or are characteristic of genes expressed in myeloid cell specific fashion (see the abstract, methods and the discussion sections).

Dropulie et al teaches a method of conditionally expressing a gene of interest in a cell using replicating viral vector and methods of prophylactic and therapeutic treatments (see the abstract). The vectors comprise a promoter driving the

expression of the gene of interest and operably linked to a polyA signal (see figures 1A-1E and 5 A-C). The patent discloses and discusses the types of genes that can be expressed using the vectors, the control elements such as promoters used in the vectors, different uses for the vector, routes of administration and other details (see columns 12-28). For example, the art teaches vectors that can conditionally replicate in macrophages and have macrophage promoters (see lines 54-65 in column 20). The art also teaches to express toxins using the vector (see lines 1-10 in column 22).

At the time of the invention, it would have been obvious to an artisan of ordinary skill to modify the vectors of Malik et al by substituting the promoters of CD156 gene, scavenger receptor gene or any other macrophage cell specific promoters with a reasonable expectation of success. An artisan of skill would have motivated to modify the vector to find the best promoter that will allow specific expression in macrophages and could be used for delivering genes to atherosclerotic tissues or cells. Additionally, an artisan could modify the vector for making conditional vectors for expressing toxins as taught by Dropulie et al.

Therefore, the claimed invention as a whole would have been *prima facie* to one of ordinary skill in the art at the time the invention was made in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments with respect to claims 1-1-3 and 5-31 have been considered but are moot in view of the new ground(s) of rejection.

10. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

Ram R. Shukla

RAM R. SHUKLA, PH.D
PATENT EXAMINER

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632